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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,306	12/08/2000	Margaret A. Schwarz	9022.20	3192

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MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/733,306	SCHWARZ, MARGARET A.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-02-06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-11,17-19,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-11,17-19,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

3. Applicant's arguments with respect to the rejection claims 1-2, 7-11, 17-19 and 47-48, under 35 USC 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Specification

4. The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. (see page 8, 2nd paragraph.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6-14, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The instant claims are drawn to methods of facilitating vascular growth in cardiac muscle of a human subject comprising inhibiting the activity of EMAP II of SEQ ID NO: 4

in said human subject by administering an antibody that specifically binds to EMAP II of SEQ ID NO: 4.

The specification discloses only antibodies such as monoclonal and polyclonal antibodies generated from the peptide consisting of the amino acid sequence DAFPGEPDKELNP sequence wherein the antibody binds specifically to human endothelial-monocyte activating polypeptide II. However, the scope of the instant invention encompasses the "polyclonal, monoclonal antibodies, antibody fragments, humanized or chimeric antibodies that retain the combining region that specifically binds to EMAP II," see page 4 of the specification as filed. Moreover, the specification teaches (see page 4), that the antibodies of the present invention include those of any type of immunoglobulin, including but not limited to IgG and IgM immunoglobulins. The antibodies may be of any suitable origin, such as chicken, goat, rabbit, horse, etc., but are preferably mammalian and most preferably human. The antibody may be administered directly or through an intermediate that expresses the antibody in the subject.

The specification as filed in Example I, see pages 11-12, Applicant demonstrated an improvement in myocardial function in rats comprising the administration of a rabbit EMAP II antibody, *post operatively.* Applicant concluded that the shortening fraction is improved in the EMAP II antibody group only at 28 days postoperatively. It is noted that the methods of instant claims do not recite administration of anti-EMAP II antibody following ligation of the left anterior descending artery.

In regards to the state of the prior art as of the filing date of the instant specification, the exact structure and function of EMAP II *in vivo* was unknown, as evidenced by Murray et al. (American Journal of Pathology, Vol. 157, No. 6, 2000, pages 2045-2053), and there was no guidance or teaching for the use of antibodies targeting EMAP II for the facilitation of vascular growth in cardiac muscle of a human subject afflicted with myocardial ischemia, atherosclerosis, myocardial disease, cardiomyopathy or cardiac hypertrophy, particularly for the treatment of these diseases. Therefore, Applicant's claim to methods comprising the use of antibodies targeting EMAP II appears to be incomplete, and premature since the actual structure of biologically active EMAP II was unknown as of the filing date of the instant application. Murray et al. summarized what was known in regards to the structure of EMAP II after the filing date of the instant application (see page 2046, paragraphs 2-3):

> "[F]ull-length cDNAs encoding murine and human EMAP-II have been isolated from MethA, U937, and normal peripheral blood cells, respectively. The deduced amino acid sequences seem to be 86% identical between the two species. The amino-terminal region of mature EMAP-II has minor homologies with interleukin (IL)-8, IL-1b, and von Willebrand Factor Antigen II. The cDNA sequence suggests that EMAP-II is synthesized as a 34-kd precursor molecule, which is cleaved at a critical aspartate residue to produce an18-kd mature polypeptide. The putative precursor, 34-kd EMAP-II, lacks a classic hydrophobic signal peptide necessary for membrane translocation, indicating that the mature molecule may be secreted by a novel pathway; *however, little is known about the mechanism of this processing or its control.* It has been suggested that EMAP-II may be processed in a similar manner to the leaderless precursor of IL-1b, which undergoes proteolytic cleavage at the plasma membrane with subsequent release into the extracellular space.
>
> *The relationship between the mature form of EMAP-II and the putative precursor as described by Kao et al. has recently become less clear*, since Quevillon et al. have noted the high degree of amino acid identity between EMAP-II and the p43 auxiliary component of the mammalian multisynthase complex. This complex is a high-molecular weight structure composed of nine aminoacyl-tRNA synthetases and three auxiliary proteins with molecular weights of 18, 38, and 43 kd. Hamster p43 component is composed of 359 amino acids with a predicted molecular weight of 40 kd. This protein

shares and 85% amino acid identity with human and murine 34-kd EMAP-II, respectively, whereas the human p43 and EMAP-II homologues seem to share 100% identity. We recently reported the isolation of recombinant human EMAP-II and have raised polyclonal antibodies against this material. In Western blots, the antibodies detect a 34-kd EMAP-II precursor molecule in lysates of U937 cells as well as an 18- to 20-kd mature form. Both 34- and 18- to 20-kd species can be detected in culture medium conditioned by U937 cells. Significantly; our antibodies fail to detect a protein band in the region of 40 to 43 kd, corresponding to a putative human p43."

Murray et al. further note that the distribution of the EMAP II protein *in vivo* was not known prior to their studies (see page 2046, 4th paragraph). Immunohistochemical analysis of EMAP II distribution revealed occasional weak cytoplasmic staining of endothelial cells in lung, heart, cervix, ovary, and small and large intestine, although in general blood vessels of all sizes were negative. *In the heart there was weak cytoplasmic staining of muscle*, with darker staining of some capillaries (see page 2049, paragraph 3).

Moreover, Schwarz et al. (1999) concluded that EMAP II is highly expressed in the murine embryonic developing lung, however EMAP II is localized to the large vessels during the vascular stage and through adulthood (see page L374). However, there is no clear and specific role indicated for EMAP II in cardiac muscle. Moreover, the data of Schwarz et al. suggested a role for EMAP II as a director of *neovascularization* in the developing lung, however it was concluded that *further experimentation* was required to determine the role of EMAP II in the control of vascular growth in adulthood (see concluding paragraphs on page L374). In other words, there was no clear guidance given in the prior art for the use of antibodies targeting EMAP II

in cardiac muscle cells, particularly for the facilitation of vascular growth *in vivo,* and further in a patient suffering from a cardiac disorder.

Thompson et al. describe a potential role for antiangiogenic proteins in the myocardial infarction repair process. However, the disclosure of the Thompson et al. reference suggests that the biologically active form of EMAP II is not consistent in all mammals. For example, see page 162, 1st col, 1st paragraph of Thompson et al. set forth below:

> Following myocardial infarction, there is a marked and sustained elevation of EMAP II protein. Western analysis of EMAP II suggests that its proform, preactivation and cleavage, is the predominate isoform in the infarct region. Although those factors that activate and cleave EMAP II are unknown, it is presumed that levels of its potent cleaved mature form of EMAP II are either transiently expressed or in low quantities that are difficult to detect. Although cleavage of EMAP II has been attributed to interleukin converting enzymes (ICE) caspase 3 and 7 via activation of the apoptotic cascade [28, 29], despite a tremendous amount of active apoptosis within the myocardium following myocardial infarction [30–33] and caspase 3 activation [34–36], Western analysis indicates that EMAP II is expressed in its proform (34 kDa) and is not cleaved to its mature (21 kDa). Our recent report suggests that EMAP II is not a substrate for the ICE [37].
>
> Specifically, (1) mEMAP II is an active inducer of cellular apoptosis via caspase 3 induction [7] and of upregulation of the Fas-associated death domain with concomitant downregulation of Bcl-2 [12] in endothelial cells; (2) pEMAP II remains in its 34 kDa form following *in vivo* induction of apoptosis in the presence of full activation of the ICEs (including caspase 3 and 7) [37]; and (3) despite a 98% homology between the murine and human forms of mature EMAP II (and identical antiangiogenic properties of mEMAP II between the murine and human forms), the human form of EMAP II contains an alternative amino acid sequence at the proposed cleavage site that is not recognized as an ICE cleavage site. Possible explanations for the different observations of EMAP II cleavage are (1) posttranslational cleavage of EMAP II is not associated with the apoptotic pathways found following rat myocardial infarction; (2) differences in tissue types examined (kidney [29] *versus* myocardium); or (3) lack of sensitivity in our method of analysis.

This passage suggests that EMAP II can be found in two forms the mature and proforms, however it appears that the mature form (i.e. 21kDa) form is only expressed transiently, and the exact mechanism that controls the processing of the proform (i.e. 34 kDa) are unknown. Moreover, the above passage suggests that the manner in which EMAP II is processed may vary from one tissue type to the next, suggesting that different forms of the protein my control of regulate different activities in specific tissue types.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Therefore, Applicant's disclosure of a rabbit antibody to EMAP II, or an antibody targeting the amino acid sequence DAFPGEPDKELNP is insufficient since the overall structure of the biologically active form of EMAP II appears to be potentially variable from species to species, and from tissue type to tissue type.

In vitro and animal model studies have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species and model dependent, it is not clear that experimental data observed in a post-operative rat treated with EMAP II rabbit antibodies accurately reflects the relative ability or efficacy of the claimed methods of immunotherapy by administering any antibody (i.e. polyclonal, monoclonal antibodies, antibody fragments, humanized or chimeric antibodies) that retains the combining region that specifically binds to EMAP II .

Pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional

properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

See page 1338, footnote 7 of Ex parte Agrawal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively practice any method of immunotherapy or reach an appropriate beneficial therapeutic endpoint in humans by administering any EMAP II antibody or form thereof. The specification does not teach how to extrapolate data obtained from *in vitro* or *in vivo* observations as well as clinical experience with EMAP II specific antibodies to the development of effective methods of any immunotherapeutic method broadly encompassed by the claimed invention.

It is noted that experimental protocols usually are conducted under defined conditions wherein the agent and the stimulus / insult occur at the same or nearly the same time. Regulation of an immune response is much easier to achieve under such controlled conditions that experienced in the human disorders or diseases such as the immunotherapeutic methods encompassed by the claimed invention

Therefore, in view of the breadth of the claimed invention, the limited guidance in the specification as filed, and furthermore the lack of clarity in regards to the structure of biologically active EMAP II (as of the filing date of the instant application) targeted in the methods which read on treating any subject, human or otherwise, Applicants have not taught the skilled artisan how to practice the full scope of the claimed invention without undue experimentation.

7. Claims 1-4, 6-14, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

With the exception of the specific antibody that binds specifically to human EMAP II peptide CDAFPGEPDKELNP for purifying recombinant EMAP II, in the specification as filed, there is insufficient written description about the binding specificity of any and all antibodies that bind to EMAP II of SEQ ID NO: 4 for the facilitation of vascular growth in cardiac muscle of a human subject afflicted with myocardial ischemia, atherosclerosis, myocardial disease, cardiomyopathy or cardiac hypertrophy using any antibody that binds to SEQ ID NO: 4. However, the scope of the instant invention encompasses the "polyclonal, monoclonal antibodies, antibody fragments, humanized or chimeric antibodies that retain the combining region that specifically binds to EMAP II," see page 4 of the specification as filed. Moreover, the specification teaches (see page 4), that the antibodies of the present invention include those of any type of immunoglobulin, including but not limited to IgG and IgM immunoglobulins. The antibodies may be of any suitable origin, such as chicken, goat, rabbit, horse, etc., but are preferably mammalian and most preferably human.

The specification as filed discloses only a composition comprising an antibody that binds only human EMAP II peptide consisting of the amino acid sequence CDAFPGEPDKELNP, one of skill in the art would reasonably conclude that the

disclosure fails to provide a representative number of species of mammalian antibody to describe the genus of antibody of facilitating vascular growth in cardiac muscle of subject for the treatment of myocardial ischemia, atherosclerosis, myocardial disease, cardiomyopathy or cardiac hypertrophy using *any* antibody that binds to SEQ ID NO: 4.

See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

See also January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing

identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

In the instant case it is clear that Applicants were not in possession of the full scope of possible polyclonal or monoclonal antibodies, antibody fragments, humanized or chimeric antibodies isolated form any suitable source, such as chicken, goat, rabbit, horse, etc., wherein said antibody specifically binds EMAP II of SEQ ID NO: 4.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE